The Relationship Between Glycosylated Haemoglobin and Diabetic Retinopathy in Patients with Type 2 Diabetes

Tip 2 Diabetes Mellituslu Olgularda Glikozile Hemoglobin ile Diyabetik Retinopati Arasındaki İlişki

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Abstract

Diabetes mellitus (DM) is a major health problem with long-term micro and macrovascular complications. Diabetic retinopathy (DR) is a sight-threating chronic complication of diabetes mellitus in adults. In this study, we determined the frequency of DR and the relationship between HbA1c levels, duration of diabetes and BMI with DR in type 2 diabetic patients. Six-hundred eighteen type 2 diabetic patients participated in this study. In the first examination, retinopathy was evaluated by ophthalmoscopy through dilated pupil by experienced ophthalmologist. Based on their optic fundi findings they were classified into three groups; without retinopathy, had non-proliferative DR (NPDR) and had proliferative diabetic retinopathy (PDR). In addition, the patients were classified in four groups according to their HbA1c levels; below 6.0 %, between 6.1 and 6.9%; between 7.0 and 9.9%, and; above 10.0%. According to the duration of diabetes the patients were divided into three groups. First group consisted of patients who were diabetic for less than five years, the second group consists of patients who had diabetes for a period 6-10 years and the third group, who were diabetic for more than 10 years. All patients were divided into four groups according BMI; lower 25 kg/m^2, between 25.1 and 29.9 kg/m^2, between 30 and 39.9 kg/m^2 and over 40 kg/m^2. In our study, the frequency of DR was 46.6% [28.8% have NPDR and 17.8% have PDR]. There was a stastically significant relationship between HbA1c levels and DR (both NPDR and PDR) ($p<0.000$). The frequency of retinopathy (both background and proliferative) was 4.8% in the group of diabetics with a mean HbA1c level <6%, 8.7 % in those between 6.1 and 6.9%, 62.8% in those between 7 and 9.9% and 82.2% in those exceeding a mean HbA1c level of 10%. According to our results, there was a significant relationship between duration of diabetes and DR (both nonproliferative and proliferative) ($p<0.001$). A similar relationship between PDR and BMI ($p<.001$), between NPDR and BMI ($p<.01$) was found. But there was no relationship between gender and DR ($p=0.51$). These results imply that duration of diabetes, HbA1c level and BMI are important risk factors for onset or progression of DR in type 2 DM. Therefore decrease in HbA1c values and BMI prevent or delay the onset/or progression of DR. *Turk Jem 2007; 11: 10-5*

Key words: Diabetes mellitus (DM), diabetic retinopathy (DR), diabetic microvascular complications, glycosylated haemoglobin, HbA1c,

Özet

Diabetes mellitus (DM) oluşturmuş olduğu uzun süreli mikrovasküler ve makrovasküler komplikasyonları ile önemli bir sağlık sorunudur. Diyabetik retinopati (DR), diabetes mellitusun görmeyi tehdit ettiği kronik bir komplikasyonudur. Bu çalışmada tip 2 diabetik olgularda DR'nin sıklığını ve DR ile HbAıc düzeyleri, diyabet süresi ve beden kitle indeksi (BKI) arasındaki ilişkiyi araştırmayı amaçladık.

Çalışmaya 618 tip 2 diabetik hasta alınmıştır. İlk muayenelerinde göz hastalıkları uzmanları tarafından pupiller dilatasyon sağlandı ve oftalmoskop ile göz dibi bakıları yapıldı. Olgular fundus bakısına göre retinopatinin bulunmadığı, non-proliferatif DR (NPDR) ve proliferatif retinoapti (PDR) olmak üzere üç gruba ayrıldı. Ayrıca, olgular HbAıc düzeyine göre %6'nın altı, %6.1-6.9,%7.0-9.9 ve %10'nun üzeri olmak üzere dört grupta toplandı.

Diyabet süresine göre ise hastalar üç gruba ayrıldı. Diyabet süresi birinci grupta beş yılın altında, ikinci grupta 6-10 yıl arasında ve üçüncü grupta ise 10 yılın üzerinde idi. Çalışmaya alınan hastalar BKI 'ine göre <25 kg/m^2, 25.1-29.9 kg/m^2, 30-39.9 kg/m^2 ve >40 kg/m^2, olmak üzere dört grupta değerlendirildi.

Çalışmamızda DR'nin sıklığı %46.6 (%28.8 NPDR ve %17.8 PDR) olarak bulundu. HbAıc düzeyi ile hem NPDR hem de PDR arasında istatiksel

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yönden anlamlı bir ilişki saptandı (p<0.000). DR (hem NPDR , hem de PDR) sıklığı, HbAıc düzeyi %6'nın altında olan hastalarda %4.8, %6.1-6.9 arasında % 6.1, %7-9.9 arasında % 62.8 ve %10'nun üzerinde ise %82.2 olarak bulundu.
Çalışmamızın sonuçlarına göre, diyabet süresi ile her iki DR (NPDR ve PDR) arasında istatiksel olarak anlamlı bir ilişki (p<0.001) saptandı. Benzer anlamlı ilişki PDR ile BKI (p<0.001) ve NPDR ile BKI (p<.01) arasında da gözlendi. Ancak, cinsiyet ile DR arasında herhangi bir anlamlı ilişki bulunmadı (p=0.51)
Çalışmamızın verileri, tip 2 diabetes mellituslu olgularda DR'nin başlaması veya ilerlemesi üzerinde diyabet süresi, HbAıc ve BKI'nin etkin rol oynadığını ortaya koymuştur. Bu nedenle HbAıc değerlerinin düşürülmesi, BKI'nin azaltılması ile DR'nin başlaması veya ilerlemesi önlenebilir veya geciktirilebilir. *Turk Jem 2007; 11: 10-5*
Anahtar kelimeler: Diabetes mellitüs (DM), diyabetik retinopati (DR), diyabetik mikrovasküler komplikasyonlar, glikozile hemoglobin, HbAıc.

Introduction

Type 2 diabetes mellitus (DM) is by far the most prevalent endocrine disease. It is expected doubled in the next two decades. Changing lifestyle, especially increasing weight caused by nutritional excess and decreasing physical activity play important role for increasing of type 2 diabetes (1,2) .
Many people with type 2 diabetes have macrovascular and microvascular complications such as diabetic retinopathy (DR) at the time of first diagnosis of diabetes (3-6) .
DR is the most frequent cause of blindness among adults aged 20-75 years and it remains a significant health problem worldwide as reported by the ADA (7). Improvements in diabetic care and earlier detection of the disease can reduce the incidence of visual impairment and blindness (8,9). By the time of clinical diagnosis of type diabetes, some individuals already show evidence of DR, indicating that diabetes may have been present for several years (10).
Duration of diabetes, glycemic control, hypertension, dyslipidemia, obesity, proteinuria, pregnancy and socio-economic status play important role for development of Dr. Duration of diabetes and inadequate glycaemic control are most important (11).
Currently, monitoring HbA1c levels is the gold standard for assessing average blood glucose concentration over three months (3,8,9,13-15). The target level of HbA1c which is needed for adequate glycemic control in type 2 DM is unknown.
The aim of the present study was to assess frequency of DR and the relationship between HbA1c levels, duration of diabetes, BMI and DR in the patients with type 2 diabetic patients.

Subjects and Methods

All diabetic patients, examined in the Endocrinology Clinic of Celal Bayar University Medical Center between December 2002 and May 2005, were participated in this study. All patients included in the study were admitted our polyclinic for the first time. Six-hundred eighteen type 2 diabetic patients (average age (mean ± SD): 54.43 ± 11.51 years, duration of diabetes 9.46 ± 6.2 years, BMI 29.67 ± 5.08 kg/m^2) participated in this study. Our inclusion criteria for the classification and diagnosis of DM were the new set criteria for diabetes adapted by American Diabetes Association (ADA) by in 1997 (1). Patients with secondary diabetes (acromegaly, Cushing's syndrome e.g) were not included in this study. In the first physical examination, each patient body mass index (BMI) was calculated and HbA$_{1c}$ level measured.
Eye examinations of the patients were conducted by three experienced opthalmologists. All patients had a direct opthalmoscopic examination at baseline performed by dilatation of pupils by opthalmogists who had no knowledge of the patients' characteristics.
The earliest lesion visible with opthalmoscope are termed non-proliferative DR (NPDR), including microaneurysms, haemorrhages, hard exudas, cotton wool spots, intraretinal microvascular abnormalities and venous beading. The proliferative DR (PDR) is characterised by growth of new vessels on or within one disc diameter of the disc are termed new vessels on the disc and in other locations, new vessels elsewhere.
Based on their optic fundi findings they were classified into three groups; without DR (normal group), NPDR and PDR.
Fasting venous blood samples were obtained for the determination of HbA$_{1c}$. HbA$_{1c}$ value were consists of four groups; <6.0%, between 6.1% and 6.9%, between 7.0% and 9.9% and over 10%.
According to the duration of diabetes the patients were divided into three groups. First group consisted of patients who were diabetic for less than five years, the second group consists of patients who had diabetes for a period 6-10 years and in the third group, who were diabetic for more than 10 years.
All patients were divided into four groups according BMI; lower 25 kg/m^2, between 25.1 and 29.9 kg/m^2, between 30 and 39.9 kg/m^2 and over 40 kg/m^2.
HbA$_{1c}$ levels were measured using an immunoturbidimetric assay kit (Roche Diagnostic, Germany) on a Hitachi 704 analyzer (Hitachi, Toyo, Japan).
Statistical Analysis
Statistical analyses were performed using the SPSS package (SPSS for Windows Version 10.0, Chicago, USA). All values were expressed as mean ±S.D. Chi-square tests were used to compare categorical variables between groups of subjects. Regression analysis was performed to find out effective factors for the relationship between DR and, HbAıc and BMI and duration of diabetes. P value<0.05 considered to be statistically significant.

Results

The clinical characteristics of the patients are shown Table 1. In all patients the mean HbA1c level was 9.12 ± 2.8%. 104 (16.8%) patients had a HbA1c value of <6.0%, 137 (22.1%) between 6.1% and 6.9%, 195 (31.5%) between 7.0% and 9.9% and 182 (29.4%) over 10% (Table 2).

In this study, the frequency of DR was 46.6% (28.8% have NPDR and 17.8% have PDR). The frequency of diabetic (both NPDR and PDR) retinopathy was lowest in the group of diabetes with the lowest HbA1c concentration <6% (4.8% or 5/104), 8.7% or 12/137 in the group with HbA1c values between 6.1% and 6.9%, 62.8% or 121/195 in the group with HbA1c values between 7% and 9.9% and highest (82.2% or 150/182) in the group with HbA1c concentrations over 10% (Table 2). As seen by the logistic regression analysis, in patients who had HbA1c value of 7%-9.9% there were significant relationship between DR and HbA1c levels (p=0.001). According to the duration of diabetes in the first group the frequency of DR was 20.2 %, with 50 patients NPDR and 8 with PDR, in the second group the frequency of DR was moderately higher 82 (23.4%), with 61 patients with NPDR and 21 patients with PDR. Finally, in the last group the frequency of DR was highest (56.4%). 67 patients with NPDR and 82 patients with PDR. Our results shown that there was significant relationship between the duration of diabetes and DR (p<.001; Table 3).

Table 1. Clinical and funduscopic characteristics of the all patients

Age (years)		**54.43 ± 11.5**			
Gender					
	Male	41.4% (n=256)			
	Female	58.6% (n=362)			
Duration of Diabetes (years)		9.46 ± 6.2			
BMI (kg/m^2) (mean ±SD)		29.6 ± 5.0			
Funduscopic examination	Female n (%)	Male n (%)	c^2	df	p
No DR	205 (53.3%)	125 (52.2%)			
NPDR	116 (31.8%)	62 (29.4%)	1.550	2	0.432
PDR	62 (14.9%)	48 (18.4%)			
		All diabetic patients (n=618)			
No DR		330 (53.4%)			
NPDR		178 (28.8%)			
PDR		110 (17.8%)			

DR= Diabetic retinopathy, NPDR= Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopath

Table 2. Relationships between HbA1c levels and presence of diabetic retinopathy

HbA1c levels (%)	n	Presence of retinopathy (%)
<6.0	104 (16.8%)	4.8 % (n=5)
6.1-6.9	137 (22.1%)	8.7% (n=12)
7.0-9.9	195 (31. 5 %)	62.8% (n=121)
>10.0	182 (29.4%)	82.2% (n=150)

Table 3. Relationships between the duration of diabetes and frequency of diabetic retinopathy

Duration of Diabetes (years)	n	Prevalence of retinopathy %	Funduscopic Examination n
<5 years	291 (47.2%)	20.2 %	n= 233 No retinopathy * n=50 NPDR* n= 8 PDR*
6-10 years	143 (23.1%)	23.4 %	n= 42 No retinopathy * n= 61 NPDR* n=149 PDR *
> 10 years	184 (29.7%)	56.4 %	n=35 No retinopathy * n=67 NPDR * n=82 PDR *

(Chi-Square tests :c2 =72.77,1 df= 2, * p<0.001)
NPDR= Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy

As a result of logistic regression analysis, it is being observed that in the first group there was no difference between the two groups which include age,gender and BMI.But in the second group which include duration diabetes it was found that the most important variables that affect DR is having HbAıc 7%-9.9 (odds ratio (OR) (95% CI (confidence interval) 0.015 (0.004-0.064) and having duration of diabetes over 10 years (odds ratio (OR) (95% CI (confidence interval) 3.71 (1.008-13.676).

Similarly, our data revealed a significant relationship between BMI and PDR (p<.001) and a significant relationship between BMI and NPDR (p=.01) (Table 4). This study also demonstrated that patients with PDR had the highest mean BMI (Figure 1). While no relationship was observed between gender and DR (p=,432).

Discussion

DR is a specific microvascular complication of both type 1 and type 2 diabetes. Duration of diabetes and hyperglycemia are two well-known risk factors for the development of DR. Up to a fifth of newly diagnosed type 2 diabetics have been found to have DR (17-20) .

High glucose concentrations and chronic hyperglycemia is now accepted as the common pathway leading DR. A number of plausible biochemical pathways linking glucose metabolism directly to the development of DR: the aldose reductase pathway, increased protein kinase C activity with increased vasodilatory prostaglandins production, increased non-enzymatic glycation and glucose induced auto-oxidative damage (21). Increased blood retinal barrier permeability and alterations in retinal blood flow may also be important in the pathogenesis. In short, biochemical, haemodynamic and hormonal mechanism may interact together to produce the typical lesions of vascular occlusion, microaneurysms, haemorrhages, hard exudates and new vessels (neovascularization) (11, 18-22).

Table 1 shows that in our study the frequency of DR was 46.6% (28.8% have NPDR and 17.8% have PDR). Our results are higher than that observed in Caucasians with type 2 DM from the United States (39%) and from South Africa (41%) and lower than that found in Caucasians from New Zealand (60%) and Caucasian from the South of Brazil (47%) (23). Internationally, the frequency of retinopathy has varied widely depending on the methodology and population sample.

Table 4. The relationship between body mass index (BMI) and frequency of diabetic retinopathy

BMI (kg/m²)	Fundi examination	p
24.4 ± 4.0	No diabetic retinopathy	
28.1 ± 4.52	NPDR	
36.5 ± 4.31	PDR	
No diabetic retinopathy vs NPDR		0.01
No diabetic retinopathy vs PDR		<0.001
NPDR vs PDR		0.4
NPDR= Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy		

The known duration of diabetes is one of the most important factor determining the presence of DR (11,24). Our data indicate an association between longer duration of diabetes and increased frequency of retinopathy. NPDR and PDR frequency increased in the group who was diabetic for than ten years (p<.001). Similarly, Vinker et al (24) and Romera et al (25) stated that longer duration of diabetes have increased DR.

Many clinical trial results from the Diabetes Control and Complications Trial (DCCT) (8,22) and the epidemiological data from the Wisconsin Epidemiological Study of DR (WESDR) have emphasized the strong relationship of glyceamic control the development and progression of DR (26-30). In an other study, Australian Diabetes Society, reported that the patients with DR had a significant higher HbA1c levels (31).

Today, HbA1c measurement is regarded as the "gold standard" indicator for glycaemic control in diabetic patients, reflecting glucose levels over a 2-3 months period (2,12). The American Diabetes Association (ADA) recommends that the mean HbA1c value should be kept below 7% to prevent diabetic micro and macrovascular complications (32).

In this study the frequency of (both NPDR and PDR) retinopathy was low (4.8%) in the group with mean HbA1clevel less 6.0% while, in the group with a mean HbA1c level over 10%, the frequency highly increased (82.2%). Our data demonstrate a correlation of lower HbA1c levels with a lower frequency of DR. Reductions in blood glucose or HbA1c concentrations through tight blood glucose control in people with diabetes reduces the rate of progression microvascular complications such as DR, neuropathy and nephropathy (12,31-35).

Similarly, our findings revealed a significant relationship between BMI and PDR (f=22.04, p<.001) and a significant relationship

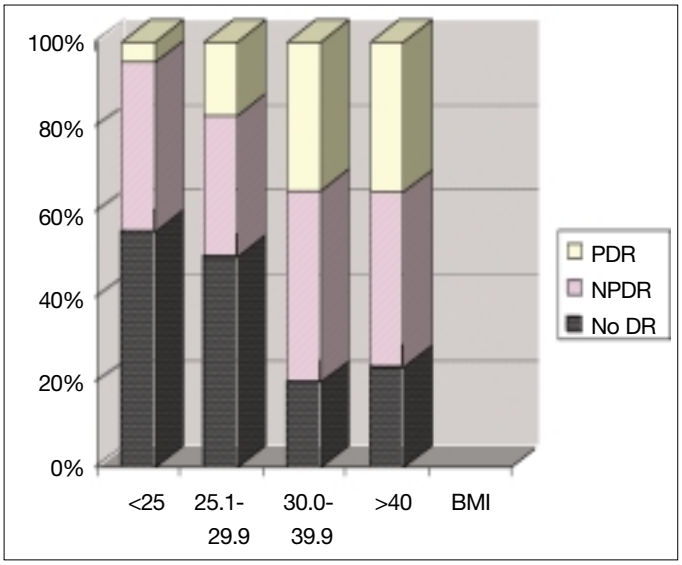

Figure 1. Frequency of diabetic retinopathy according to the body mass index (BMI)

NPDR= Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy

between BMI and NPDR (f=16.18, P=.01). This study also demonstrated that patients with PDR had the highest mean BMI. Knuiman et al. (35) and Santos et al. (23) stated that high BMI has been cited as an important factor for the presence of DR . Our results are similar to Knuiman et al. because in the PDR group the mean BMI was the highest (35.31 ±5.1 kg/m^2). But Nakagami et al. (36) did not find a significant relationship between DR and BMI.

In this study, there was no relationship between gender and DR (p=,432). Nakagami et al. (36) and Tapp et al. (10) stated that they did not find a significant relationship between gender and DR. But Vinker et al. (24), stated that in the laser treatment group, the male to female ratio was double. Santos et al (23) shown that there was a trend toward a higher frequency of DR in men than in women.

In Conclusion: This study stated that the frequency of DR was 46.6% (28.8% have NPDR and 17.8% have PDR). There was strong relationship between duration of diabetes and DR (p<.001) and a similar relationship between BMI and PDR (p<.001), between BMI and NPDR (P=.01). But we did not find any connection between gender and DR (p=,432).

In our study of the 241 (38.9%) diabetic patients had mean ADA recommendations HbA1c value. These patients had newly onset of diabetes, mild hyperglycemia and BMI of>30 kg/m^2.

Our findings contribute that decreasing in HbA1c values or achieving ADA criteria can prevent or delay the onset/or progression of microvascular complications such as retinopathy. Because DR is a serious diabetic microvascular complication. Regular screening for diabetic retinopathy and tighter glycaemic control could reduce the number of people who develop vision-threating retinopathy.

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